Denervation, Hyperinnervation, and Interactive Regulation of Dopamine and Serotonin Receptors[a]

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In adult experimental animals, 6-hydroxydopamine (6-OHDA) lesions that destroy more than 90% of the dopamine (DA) afferents to the neostriatum entail a dysfunction that resembles Parkinson's disease in the human.[1–3] Sensorimotor neglect, aphagia, adipsia, cognitive alterations, and postural abnormalities characterize this behavioral syndrome in the rat.[3–6] Even after severe nigrostriatal 6-OHDA lesion, however, considerable recovery of function may occur, associated with modified properties of the spared DA terminals, including increases in DA synthesis,[7,8] metabolism,[9] and fractional efflux.[10] Supersensitivity of neostriatal DA receptors has also been reported as another factor accounting for some functional recovery in these animals.[11,12] On the other hand, following an extensive nigrostriatal DA denervation but carried out in neonates, the rats reach adulthood with only minor sensorimotor and ingestive deficits.[13,14] Among mechanisms underlying this functional sparing, a major reorganization of the neostriatal circuitry has been proposed, as evidenced by the striking serotonin (5-HT) hyperinnervation that then takes place in the rostral half of neostriatum.[15–18] Moreover, autoradiographic evidence has been obtained suggesting that up-regulation of certain 5-HT receptors might be associated with 5-HT hyperinnervation, at least in conditions of homotypic sprouting after 5,7-dihydroxytryptamine lesion.[19] The neonatally 6-OHDA-lesioned rat provided an interesting opportunity to investigate eventual regulations of DA and 5-HT receptors in a model of 5-HT hyperinnervation unassociated with prior lesion of the 5-HT system. We therefore used quantitative autoradiography after radioligand binding to examine the amount and distribution of dopamine D_1 and D_2 receptors and of some of the known 5-HT receptor subtypes, in the brain of adult rats subjected to nigrostriatal 6-OHDA lesion soon after birth. It was expected that the localization of eventual changes within the neostriatum and related brain regions

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TABLE 1. Concentration of Aromatic Monoamines in the Neostriatum of Control and Neonatally 6-OHDA-Lesioned Rats[a]

Region	DA	DOPAC	HVA	3-MT	5-HT	5-HIAA
Rostral neostriatum						
Control	99.7 ± 8.8	65.6 ± 9.7	14.3 ± 1.0	6.6 ± 1.0	3.3 ± 0.40	7.4 ± 1.0
Lesioned	0.04 ± 0.02	0.50 ± 0.20	0.10 ± 0.02	0.10 ± 0.01	5.2 ± 0.80	24.1 ± 3.0
% change	↓ 99.9 ***	↓ 99.3 ***	↓ 99.2 ***	↓ 98.6 ***	↑ 56.8 ***	↑ 225.7 **
Caudal neotriatum						
Control	46.3 ± 9.3	34.7 ± 7.2	7.4 ± 1.0	4.2 ± 0.70	9.5 ± 1.2	24.4 ± 5.0
Lesioned	0.30 ± 0.09	0.90 ± 0.20	0.10 ± 0.05	0.10 ± 0.02	9.8 ± 1.3	30.7 ± 3.5
% change	↓ 99.3 ***	↓ 97.4 ***	↓ 98.1 ***	↓ 98.6 ***	↑ 3.2 n.s.	↑ 25.8 n.s.

Abbreviations: DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 3-MT, 3-methoxytyramine; 5-HT, serotonin; 5-HIAA, 5-hydroxyindole-3-acetic acid.

[a]Values are mean ± SEM ($n = 12$) in ng/mg protein. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$, by Student's t test. (From Dewar *et al.*[22] Reproduced, with permission, from *Brain Research.*)

might shed some light on possible regulatory interactions between these two monoamine systems.

MONOAMINE METABOLISM IN ADULT NEOSTRIATUM AFTER NEONATAL 6-OHDA LESION

The experiments were carried out in normal control and adult Sprague-Dawley rats (Charles River, Montreal) subjected as 3-day-old pups to bilateral intraventricular administration of 6-OHDA (Sigma, St. Louis, MO). Fifty micrograms of 6-OHDA (free base) were delivered in each lateral ventricle after systemic pretreatment with desipramine (Sigma), to protect noradrenaline neurons.[20–22]

As repeatedly demonstrated after such lesions,[3,15,17,22–26] the neonatal administration of 6-OHDA led to profound depletions of DA and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3-MT), in the neostriatum of 3-month-old animals (TABLE 1). Similar depletions have been documented as early as 15 and 30 days after the 6-OHDA lesion[22] and up to six months.[23] It has also been shown recently that, 1 and 3 months after the lesion, specific [^{3}H]BTCP binding to neostriatal DA uptake sites was reduced to about 2% of control values.[26] In this latter study, the synthesis rate of DA in the spared DA terminals was confirmed to be greatly enhanced, and neostriatal DA catabolism was found to be switched from DOPAC to HVA production.[26] Such a change presumably reflected a higher fractional release of DA together with a decreased capacity for DA uptake, leading to preferential extracellular DA degradation by catechol-O-methyltransferase as opposed to intraneuronal degradation by MAO.

In the case of 5-HT, considerable increases in 5-HT and 5-hydroxyindole-3-acetic acid (5-HIAA) levels were measured in the rostral but not the caudal half of neostriatum (TABLE 1). In two separate studies, such increases were already apparent after 1 month of survival.[22,26] The most recent investigation also indicated that neither 5-HT synthesis nor catabolism were concomitantly affected. However, inas-

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much as the density of specific [^{3}H]citalopram binding to neostriatal 5-HT uptake sites was not significantly increased at 1 month, and less increased than the corresponding 5-HT concentration at 3 months, it was concluded that the amount of 5-HT per 5-HT terminal had risen prior to the 5-HT hyperinnervation and remained elevated thereafter.[26] Such an elevation in 5-HT steady-state level might be the result of an inhibition of 5-HT release mediated by 5-HT_{1B} autoreceptors (see below).

QUANTITATIVE DISTRIBUTION OF MONOAMINE RECEPTORS AFTER NEONATAL 6-OHDA LESION

Dopamine D_1 and D_2 as well as serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1nonAB}, and 5-HT_{2A} receptors were measured by quantitative autoradiography according to well-established procedures.[23,24,27–29] Details of the respective incubation conditions are given in legends of TABLES 2–7. After incubation, film autoradiographs were prepared and exposed for 3 days ([^{125}I] ligands) or several weeks ([^{3}H] ligands). Densitometric readings were made with an image analysis system (MCID™, Imaging Research, Ontario, Canada), in the rostral and caudal halves of neostriatum and other anatomical regions of interest, selected according to the receptor subtype investigated. Standard curves from [^{3}H]- or [^{125}I]-Microscales™ were used to convert density levels into femtomoles per milligram of protein (fmol/mg protein). Multiple readings (6–25) were made in each region and the mean density measured from at least six sections per region per rat. Nonspecific binding was determined in adjacent sections and specific binding obtained by subtracting nonspecific from total binding. Each receptor subtype was studied in at least four lesioned and four control rats.

Decreased D_1 Receptors in Rostral Neostriatum

As shown in FIGURE 1, the density of dopamine D_1 receptors labeled with [^{3}H]SCH 23390 was uniformly high in the rostral neostriatum of controls, and less dense in the caudal half of neostriatum as well as in the substantia nigra. In neonatally lesioned rats, there was a slight decrease by comparison to control in the rostral but not the caudal half of neostriatum (TABLE 2). A slight apparent increase in the substantia nigra of lesioned rats was not statistically significant.

TABLE 2. D_1 Receptors in Control and Neonatally 6-OHDA-Lesioned Rats

Region	Control	Lesioned	% Change
Rostral neostriatum	1912 ± 37[a]	1500 ± 213	↓ 22[b]
Caudal neostriatum	1299 ± 135	1300 ± 141	0
Substantia nigra	1304 ± 229	1484 ± 175	↑ 13

NOTE: Dopamine D_1 receptors were labeled with the antagonist [^{3}H]SCH 23390 (DuPont, 73.2 Ci/mmol). Sections were first preincubated at 25 °C for 30 min in 50 mM Tris-HCl buffer (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. They were then incubated for 60 min in the same buffer with 1 nM [^{3}H]SCH 23390 in the presence of 100 nM of ketanserin to prevent binding of the ligand to 5-HT receptors. Nonspecific binding was determined in adjacent sections incubated with the radioligand in the presence of 30 μM (±)SKF 38393 hydrochloride.[22,24] Values are mean ± SD in fmol/mg protein. (From Radja *et al.*[24] Reproduced, with permission, from *Neuroscience.*)

[a] $p < 0.001$ for caudal versus rostral neostriatum, by Student's t test.

[b] $p < 0.01$ for lesioned versus control, by Student's t test.

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TABLE 3. D_2 Receptors in Control and Neonatally 6-OHDA-Lesioned Rats

Region	Control	Lesioned	% Change
Rostral neostriatum			
Dorsolateral	175 ± 13	223 ± 20	↑ 27[a]
Dorsomedian	126 ± 10	162 ± 25	↑ 28[b]
Ventrolateral	161 ± 8	198 ± 8	↑ 23[a]
Ventromedian	116 ± 9	128 ± 26	↑ 10
Caudal neostriatum			
Dorsal	84 ± 9	102 ± 10	↑ 21[b]
Medial	120 ± 6	153 ± 22	↑ 27[b]
Ventral	137 ± 25	193 ± 29	↑ 41[b]
Substantia nigra	66 ± 4	13 ± 7	↓ 80[a]

NOTE: Dopamine D_2 receptors were labeled with the antagonist [^{3}H]raclopride (DuPont, 63 Ci/mmol). Sections were first preincubated at 25 °C for 30 min in 50 mM Tris-HCl buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl, and then incubated for 60 min in the same buffer with 2 nM [^{3}H]raclopride. Nonspecific binding was determined in adjacent sections incubated with the radioligand in the presence of 300 μM (±)sulpiride.[22,24] Values are mean ± SD in fmol/mg protein. (From Radja *et al.*[24] Reproduced, with permission, from *Neuroscience.*)

[a] $p < 0.01$ and [b] $p < 0.05$, by Student's t test.

Earlier measurements of D_1 receptor binding after neonatal 6-OHDA lesion had shown slight increases,[30] dramatic losses[31] or no changes[32,33] in the number of these sites, perhaps due to different degrees of DA denervation in different conditions of 6-OHDA administration. In those and the present studies, the DA lesions were carried out at a postnatal age when the rat neostriatum is only partly DA innervated,[34] but a *significant proportion (60–70%) of* D_1 *receptors is* already measurable.[30,35] Since major developmental changes occur during the first postnatal week, not only in the patch and matrix distribution of the neostriatal DA innervation, but also in that of its D_1 receptors,[35] the exact time when the lesion is made may be a critical factor. After 6-OHDA lesions in the adult, significant losses of D_1 receptors were observed in the neostriatum, as if independent from the presence of DA.[36] These losses are not reversed by transplantation of fetal mesencephalic neurons. On the other hand, disruption[37] or blockade[38] of DA neurotransmission has been shown to increase D_1 receptor number. The D_1 receptor decrease after neonatal DA denervation might therefore be imputable to removal of the DA innervation itself rather than to the decreased availability of DA. Indeed, following neonatal DA

TABLE 4. 5-HT_{1A} Receptors in Control and Neonatally 6-OHDA-Lesioned Rats

Region	Control	Lesioned	% Change
Lateral septum	672 ± 39	705 ± 44	↑ 5
CA1 region	530 ± 83	564 ± 67	↑ 6
Dentate gyrus	716 ± 45	666 ± 79	↓ 7
Dorsal raphe	390 ± 36	411 ± 14	↑ 6

NOTE: Serotonin 5-HT_{1A} receptors were labeled with the agonist [^{3}H]8-hydroxy-2-(di-n-propylamino)tetralin or [^{3}H]8-OH-DPAT (DuPont, 63 Ci/mmol). Sections were first preincubated at 25 °C for 30 min in 170 mM Tris-HCl buffer (pH 7.6) and then incubated for 60 min in the same buffer with 2 nM [^{3}H]8-OH-DPAT. Nonspecific binding was determined in adjacent sections incubated with the radioligand in the presence of 10 μM unlabeled 5-HT creatinine sulfate.[23] Values are mean ± SD in fmol/mg protein. (From Radja *et al.*[23] Reproduced, with permission, from *Brain Research.*)

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TABLE 5. 5-HT_{1B} Receptors in Control and Neonatally 6-OHDA-Lesioned Rats

Region	Control	Lesioned	% Change
Rostral neostriatum	8.2 ± 1.8	10.8 ± 1.0	↑ 32[a]
Caudal neostriatum	7.2 ± 1.9	9.6 ± 0.9	↑ 33[a]
Substantia nigra	24.7 ± 3.5	38.0 ± 7.4	↑ 54[b]
Globus pallidus	22.7 ± 4.2	30.3 ± 4.3	↑ 33[a]
Dorsal subiculum	28.1 ± 6.5	28.2 ± 5.1	0

NOTE: Serotonin 5-HT_{1B} receptors were labeled with the antagonist [^{125}I]cyanopindolol (DuPont, 2200 Ci/mmol). Sections were first preincubated at 25 °C for 30 min in 170 mM Tris-HCl buffer (pH 7.6) containing 150 mM NaCl, and then incubated for 120 min in the same buffer with 12 pM [^{125}I]cyanopindolol. Nonspecific binding was determined in adjacent sections incubated with the radioligand in the presence of 10 μM unlabeled 5-HT creatinine sulfate.[23] Values are mean ± SD in fmol/mg protein (From Radja *et al.*[23] Reproduced, with permission, from *Brain Research.*)

[a]$p < 0.05$ and [b]$p < 0.01$, by one-way analysis of variance.

denervation, extracellular levels of neostriatal DA have been shown to exceed the values expected from the extent of DA denervation,[39] in keeping with the increased turnover within the residual or spared DA terminals.[26]

The localization of the D_1 receptor decrease to the rostral half of neostriatum suggested a relationship with the 5-HT hyperinnervation that also predominates in this part of neostriatum. 5-HT has already been shown to inhibit DA release from neostriatal slices acting through 5-HT2A receptors,[40] which are known to be subject to up-regulation in the present model (see below). However, because the present D_1 receptor decrease takes place in a DA-denervated neostriatum, a more direct interaction at the level of the expression of the two receptors is likely to be the cause.

Although the changes in D_1 receptors were restricted to the rostral neostriatum and consisted of a down-regulation,[22,24] they were accompanied by an *increase* in the responsiveness of neostriatal neurons to the iontophoretic application of DA or the D_1 receptor agonist, SKF 38393.[24] Such an observation was in agreement with previous demonstrations of behavioral hypersensitivity to DA[41,42] and to a D_1 receptor agonist[43] after adult lesions, presumably unassociated with D_1 receptor increases.[22,32,33] This lack of correlation between sensitivity to receptor agonists and

TABLE 6. 5-HT_{1nonAB} Receptors in Control and Neonatally 6-OHDA-Lesioned Rats

Region	Control	Lesioned	% Change
Rostral neostriatum	163 ± 19	225 ± 37	↑ 38[a]
Caudal neostriatum	160 ± 33	216 ± 26	↑ 35[a]
Substantia nigra	262 ± 17	394 ± 48	↑ 50[b]
Globus pallidus	197 ± 45	212 ± 35	↑ 8
Choroid plexus	699 ± 35	727 ± 14	↑ 4

NOTE: Other serotonin 5-HT_1 receptors (nonAB) were labeled with [^{3}H]serotonin creatinine sulfate or [^{3}H]5-HT (Amersham, 25 Ci/mmol). Sections were first preincubated at 25 °C for 30 min in 170 mM Tris-HCl buffer (pH 7.6), and then incubated for 60 min in the same buffer with 2 nM [^{3}H]5-HT, 0.01% ascorbic acid, 10 μM fluoxetine and 10 μM pargyline. Pindolol (1 μM) was added to occlude 5-HT_{1A} and 5-HT_{1B} sites. Nonspecific binding was determined in adjacent sections incubated with the radioligand in the presence of 10 μM unlabeled 5-HT creatinine sulfate.[23] Values are mean ± SD in fmol/mg protein. (From Radja *et al.*[23] Reproduced, with permission, from *Brain Research.*)

[a]$p < 0.05$ and [b]$p < 0.01$, by one-way analysis of variance.

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TABLE 7. 5-HT_{2A} Receptors in Control and Neonatally 6-OHDA-Lesioned Rats

Region	Control	Lesioned	% Change
Claustrum	3.3 ± 0.4	3.5 ± 0.7	↑ 6
Nucleus accumbens	2.3 ± 0.7	2.4 ± 0.2	↑ 4
Rostral neostriatum	1.5 ± 0.3	2.4 ± 0.2	↑ 60[a]
Caudal neostriatum	2.3 ± 0.3[b]	2.4 ± 0.8	↑ 4
Choroid plexus	1.2 ± 0.1	1.3 ± 0.2	↑ 8

NOTE: Serotonin 5-HT_{2A} receptors were labeled with the agonist [^{125}I](2,5-dimethoxy-4-iodophenyl)-2-aminopropane or [^{125}I]DOI (DuPont, 2200 Ci/mmol). Sections were first preincubated at 25 °C for 30 min in 50 mM Tris-HCl buffer (pH 7.4) containing 4 mM $CaCl_2$, 0.1% ascorbic acid and 0.1% bovine serum, and then incubated for 90 min in the same buffer with 200 pM [^{125}I]DOI in the presence of 30 nM unlabeled 5-HT to occlude 5-HT_{2C} sites. Nonspecific binding was determined in adjacent sections incubated with the radioligand in the presence of 4 mM unlabeled 5-HT creatinine sulfate.[23] Values are mean ± SD in fmol/mg protein. (From Radja *et al.*[23] Reproduced, with permission, from *Brain Research.*)

[a] $p < 0.01$, by one-way analysis of variance.

[b] $p < 0.05$, for caudal versus rostral neostriatum.

receptor measurements by radioligand binding might be attributed to the presence of spare receptors in neostriatum.[44] On the other hand, the effect of DA receptor agonists might be more dependent on the efficiency of the transducing mechanisms in target neurons than on binding parameters, that is, number and/or affinity of the receptors.[45] It has also been shown that after neonatal DA denervation, D_1 receptor-coupled adenylyl cyclase activity may be enhanced without changes in the number or affinity of D_1 receptors.[33] Earlier studies in adult rats chronically treated with the D_1 receptor antagonist SCH 23390 have also shown considerable increases in adenylyl cyclase activity dissociated from a slight increase in D_1 receptors.[46] Conversely, and within a broader perspective, chronic lithium in adult rats causes important decreases in DA-activated adenylyl cyclase activity unassociated with changes in receptor antagonist binding parameters.[47] Altogether, these and other studies indicate a clear-cut dissociation between functional properties and receptor binding parameters. In the case of the neonatally 6-OHDA-lesioned rat, the behavioral hypersensitivity to DA receptor agonists,[32,48,49] as well as the increased responsiveness of neostriatal neurons to iontophoresed DA and SKF 38393,[24] may therefore depend on the activation of transducing mechanisms rather than on the properties of the receptor-ligand recognition site.

Increased D_2 Receptors

Considerable increases were found in specific [^{3}H]raclopride binding throughout the neostriatum of neonatally 6-OHDA-lesioned versus control rats (FIG. 2). These increases were significant in three quadrants of the rostral neostriatum (dorsolateral, dorsomedial, and ventrolateral) as well as in the dorsal, medial, and ventral thirds of the caudal neostriatum (TABLE 3). As previously shown,[50] medial-to-lateral and dorsal-to-ventral increasing gradients in [^{3}H]raclopride binding are respectively observed in the rostral and caudal neostriatum of controls. These gradients were still present in the increasingly labeled neostriatum after neonatal lesion. The density of D_2 receptors in the substantia nigra of the controls was about half that of the neostriatum as a whole. As already described, after adult lesions[51] [^{3}H]raclopride

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binding was markedly decreased in the substantia nigra of the neonatally 6-OHDA-lesioned rats.

The increase in neostriatal [^{3}H]raclopride binding, presumably representing an up-regulation of D_2 receptors,[22] was approximately the same in all portions of the rostral and caudal neostriatum (TABLE 3), suggesting a common regulatory mechanism operating at the same rate and/or efficiency throughout this part of brain. The widespread neostriatal increase in D_2 receptor density was not accompanied by a parallel elevation of D_2 receptor mRNA levels.[24] At the time of the lesion, D_2 receptor mRNA levels had presumably reached only 60–75% of control adult values.[52] The development of a normal expression level of D_2 receptor mRNA in the absence of DA innervation has already been reported.[53,54]

In adult rat, increases in neostriatal D_2 receptors with no changes in mRNA levels have been measured after chronic blockade with haloperidol.[52,55,56] Decreases in D_2 receptors in the neostriatum of aged rats are less severe than decreases in mRNA levels,[57] and could reflect posttranscriptional changes of this receptor.[58] Although the mechanisms implicated in the regulation of mRNA and protein levels for the D_2 receptor remain to be clarified, one can propose that the turnover of the D_2 receptor protein in the neonatal DA-denervated neostriatum is reduced, perhaps

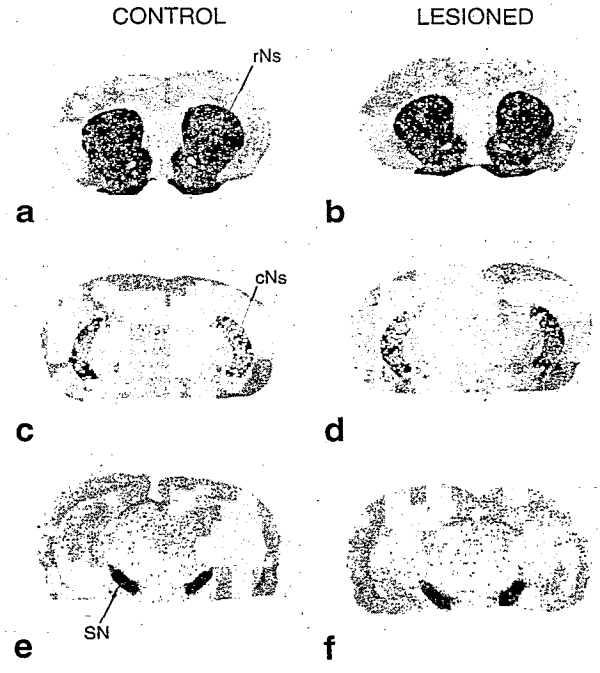

FIGURE 1. D_1 receptors ([^{3}H]SCH 23390 binding) in control and neonatally 6-OHDA-lesioned rats. In the control (**a, c, e**), D_1 receptors are abundant in both the rostral (rNS) and caudal (cNS) halves of neostriatum as well as in the substantia nigra (SN). After neonatal 6-OHDA lesion (**b, d, f**), slight but significant decreases are observed in the rNS. See TABLE 2 for quantitative data.

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because of a lack of internalization and/or removal from the neuronal membrane surface. If D_2 receptor protein synthesis is maintained at a normal rate but removal or inactivation is diminished, this will lead to an increased density of surface D_2 receptors, although not necessarily to an increased number of functional receptors, because these have to be adequately coupled to their transducing mechanisms.

The D_2 receptor increase in the neonatally DA-denervated neostriatum did not modify the sensitivity of neostriatal neurons to iontophoresed PPHT, a potent D_2 receptor agonist.[24] This observation was consistent with earlier studies showing only

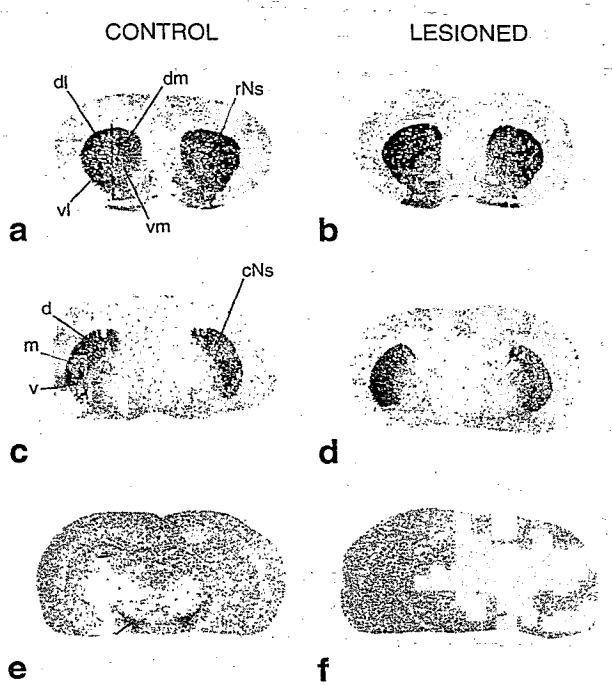

FIGURE 2. D_2 receptors ([^{3}H]raclopride binding) in control and neonatally 6-OHDA-lesioned rats. In the control (**a, c, e**), D_2 receptors show a medial-to-lateral increasing gradient in the rostral half of neostriatum (rNS), and a dorsal-to-ventral increasing gradient in its caudal half (cNS). A lower binding density is observed in the substantia nigra (SN). After neonatal 6-OHDA lesion (**b, d, f**), moderate increases are observed in both the rNS and cNS, and a marked decrease in the SN. See TABLE 3 for quantitative data.

slight increases in the behavioral sensitivity of these rats to the administration of the D_2 receptor agonist, quinpirole.[48,59] In contrast, in rats DA-denervated with 6-OHDA as adults, this same treatment was accompanied by a marked behavioral supersensitivity witnessed by locomotor changes.[32,48,49] The lesser electrophysiological and behavioral responsiveness to D_2 receptor agonists observed in the neonatally versus adult DA-denervated neostriatum raises the possibility that at least some of the increased D_2 binding sites measured after neonatal lesion are not primarily devoted to DA-mediated function. This suggestion would be in line with the former hypoth-

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esis that some of the increased D_2 receptors available for binding might not be efficiently coupled to their appropriate transducing mechanisms.

Unchanged 5-HT$_{1A}$ Receptors

Specific [^{3}H]8-OH-DPAT binding was relatively high in brain regions already described as rich in 5-HT$_{1A}$ receptors.[27,60,61] In none of these regions was this binding significantly altered 6 months after neonatal 6-OHDA lesion (TABLE 4). In the neostriatum of lesioned as well as control rats, no detectable [^{3}H]8-OH-DPAT binding was found. At the concentration of radioligand used (2 nM), only high-affinity 5-HT$_{1A}$ receptors were labeled;[62] therefore, the presence and/or changes in the number of low-affinity [^{3}H]8-OH-DPAT binding sites could not be ruled out.

The absence of 5-HT$_{1A}$ receptors in rat neostriatum[60,62] has been confirmed by immunocytochemistry[63,64] and *in situ* hybridization of the mRNA.[63,65] Homogenate binding studies have revealed the presence in neostriatum of a [^{3}H]8-OH-DPAT binding site pharmacologically distinct from the 5-HT$_{1A}$ receptor and which was decreased after 5,7-dihydroxytryptamine lesion.[66,67] In spite of the 5-HT hyperinnervation, this [^{3}H]8-OH-DPAT binding site was undetectable under the present autoradiographic conditions.

Increased 5-HT$_{1B}$ Receptors

Considerable increases were found in [^{125}I]cyanopindolol binding to 5-HT$_{1B}$ receptors in the neonatally 6-OHDA-lesioned versus control rats (FIG. 3). In the controls, as previously reported,[68,69] relatively high densities of 5-HT$_{1B}$ sites were measured in the dorsal subiculum, followed by those in the substantia nigra and globus pallidus (TABLE 5). Lower densities were detected in both the rostral and caudal neostriatum. All these regions, except for the dorsal subiculum, showed significant increases in [^{125}I]cyanopindolol binding, three months after the neonatal lesion. The highest increase was in the substantia nigra, followed by those in the globus pallidus and the two portions of neostriatum. No significant differences were present in either lesioned or control rats between rostral versus caudal halves of neostriatum. Apparent increases in the hippocampus, periaqueductal gray, and superior colliculus were not quantified, because the latter regions contain 5-HT$_{1A}$ as well as 5-HT$_{1B}$ receptors, and cyanopindolol does not distinguish between these two subtypes.[70]

The increased number of 5-HT$_{1B}$ receptors in the neonatally DA-denervated neostriatum was documented throughout this anatomical region, and similar increases were also measured in the substantia nigra and the globus pallidus, that is, the two major territories of projection of neostriatum. In rat brain, the 5-HT$_{1B}$ receptors act as terminal autoreceptors as well as receptors postsynaptic to 5-HT neurons. The neostriatal increase in 5-HT$_{1B}$ binding could not be attributed solely to an augmented number of 5-HT terminals, because it extended to both caudal and rostral halves of the neostriatum, and neither the substantia nigra nor the globus pallidus could be assumed to be 5-HT hyperinnervated.[71] The anatomical distribution of these increases suggested an up-regulation of the 5-HT$_{1B}$ receptors in the somata/dendrites of neostriatal projection neurons, accompanied by an increase of their axonal transport to both territories of projection. This interpretation was consistent with *in situ* hybridization data demonstrating the presence of mRNA for this receptor in the rat neostriatum, but not in substantia nigra nor globus pallidus.[72]

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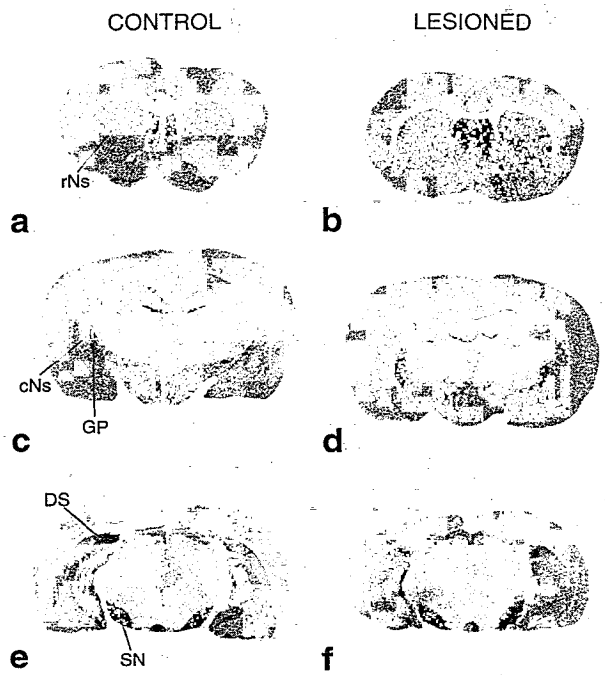

FIGURE 3. 5-HT_{1B} receptors ([^{125}I]cyanopindolol binding) in control and neonatally 6-OHDA-lesioned rats. In the control (**a, c, e**), these receptors are relatively abundant in the rostral (rNS) and caudal (cNS) neostriatum, globus pallidus (GP), dorsal subiculum (DS), and substantia nigra (SN). After neonatal 6-OHDA lesion (**b, d, f**), all these regions except the dorsal subiculum show significant increases. See TABLE 5 for quantitative data.

Inasmuch as the 5-HT_{1B} increase involved the entire neostriatum, it appeared more closely related to the overall DA denervation than the rostrally predominant 5-HT hyperinnervation, suggesting that DA afferents might normally regulate 5-HT_{1B} receptor expression, at least during early postnatal ontogenesis. However, similar DA denervations produced by 6-OHDA in adult rat do not lead to appreciable changes in 5-HT_{1B} receptors, as assessed either by quantitative autoradiography or by the electrophysiological responsiveness to the iontophoretic application of 5-HT or the 5-$HT_{1B/2C}$ receptor agonist, *m*-CPP.[73]

Increased 5-HT_{1nonAB} Receptors

In the present autoradiographic studies, 5-HT_1 sites labeled with [^{3}H]5-HT—but distinct from the 5-HT_{1A} and 5-HT_{1B} subtypes—were designated as nonAB, because both 5-HT_{1C} (now called 5-HT_{2C}) and 5-HT_{1D}, as well as other 5-HT_1 subtypes, could be labeled altogether.[74–77] No attempts were made to label 5-HT_{2C} or 5-HT_{1D} sites with [^{3}H]mesulergine or [^{3}H]5-HT in the presence of appropriate blockers, respectively, because the former compound also binds to 5-HT_{2A} receptors,[61] and the

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density of 5-HT_{1D} sites in rat brain is too low for autoradiographic detection.[77] Strong labeling of the choroid plexus did indicate binding of [^{3}H]5-HT to 5-HT_{2C} receptors,[74,75] which have been reported to be present in the neostriatum, substantia nigra, and globus pallidus of adult rat.[78] 5-HT_{1D} receptors have also been demonstrated in rat brain,[77] and appear to be postsynaptic to 5-HT fibers in the neostriatum as well as in the cerebral cortex.[77]

In the controls, 5-HT_{1nonAB} binding was the highest in the choroid plexus, followed by that in the substantia nigra, globus pallidus, and neostriatum (FIG. 4). No binding was detected in the dorsal subiculum. In the neonatally lesioned rats, both the neostriatum and the substantia nigra, but not the globus pallidus nor the choroid plexus, showed post lesion increases (TABLE 6). As was the case for 5-HT_{1B} sites, the highest increase was that in the substantia nigra, followed by equal increases in the two halves of neostriatum. However, in contrast to the 5-HT_{1B} binding, the 5-HT_{1nonAB} binding was not increased in the globus pallidus, suggesting a preferential localization of the corresponding receptors on striatonigral, as opposed to striatopallidal, projection neurons.[79] Interestingly, a similar differential localization of DA receptor subtypes on striatonigral as opposed to striatopallidal neurons has been documented

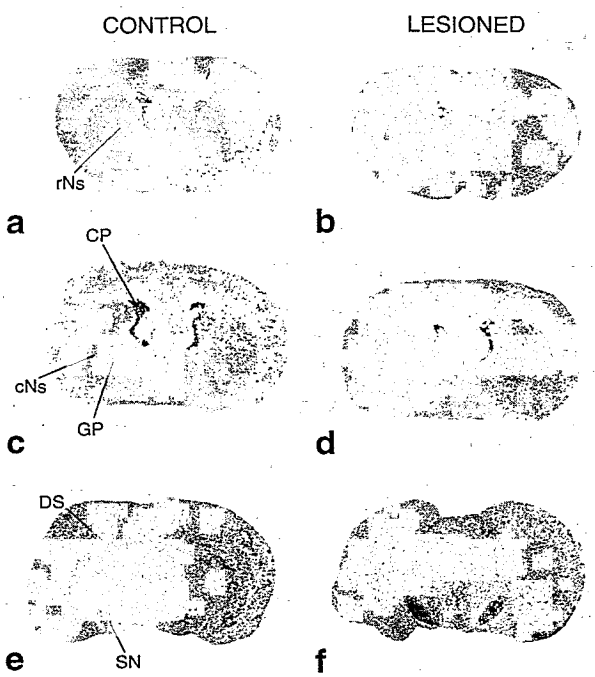

FIGURE 4. 5-HT_{1nonAB} receptors ([^{3}H]5-HT binding) in control and neonatally 6-OHDA-lesioned rats. In the control (**a, c, e**), this binding is moderate in the rostral (rNS) and caudal (cNS) neostriatum and also detectable in the globus pallidus (GP) and substantia nigra (SN). It is also prominent in the choroid plexus (CP), indicating the presence of 5-HT_{2C} receptors. After neonatal 6-OHDA lesion (**b, d, f**), increases are noticeable in the two halves of NS and in the SN. See TABLE 6 for quantitative data.

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for D_1 versus D_2 receptors, respectively.[80] It is noteworthy that, in the neonatally lesioned rats, an increase in 5-HT_{2C} receptors, together with the 5-HT_{1B} receptor increase, could account for enhanced electrophysiological responses of neostriatal neurons to the iontophoretic application of 5-HT or its receptor agonist, *m*-CPP.[73]

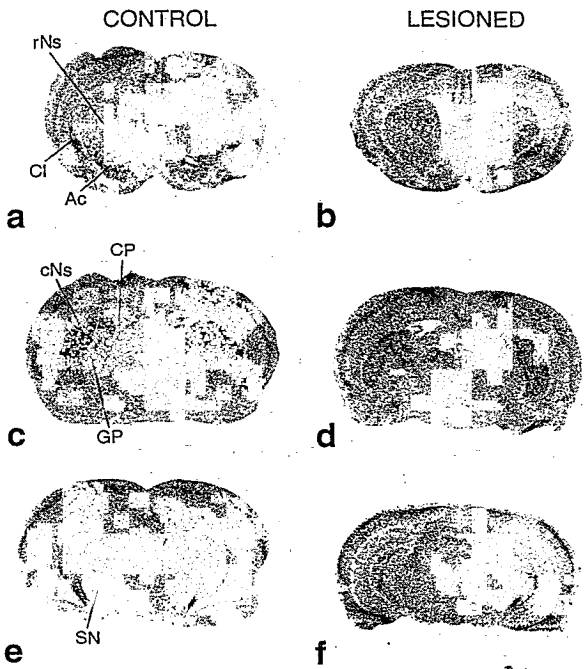

FIGURE 5. 5-HT_{2A} receptors ([^{125}I]DOI binding) in control and neonatally 6-OHDA-lesioned rats. In the control (**a, c, e**), this binding is the strongest in the claustrum (Cl) and nucleus accumbens (Ac), but also high in the caudal neostriatum (cNS); it is weaker in the rostral neostriatum (rNS) and undetectable in the globus pallidus (GP) and the substantia nigra (SN). After neonatal 6-OHDA lesion (**b, d, f**), a considerable increase is seen in the rNS. Note the moderate binding of the CP in both control and lesioned rats. See TABLE 7 for quantitative data.

Increased 5-HT_{2A} Receptors

Specific [^{125}I]DOI binding to 5-HT_{2A} receptors was markedly increased by comparison to control in the rostral neostriatum of the neonatally 6-OHDA-lesioned rats (FIG. 5). In all regions examined, this binding was relatively weak. As previously reported,[81] a laminar distribution could be observed in the neocortex, with a conspicuous band of relatively high density at the level of layer Va (FIG. 5). Overall, [^{125}I]DOI binding was the highest in the claustrum, moderate in the caudal neostriatum and nucleus accumbens, and low in the rostral neostriatum and choroid plexus (TABLE 7). Three months after the neonatal 6-OHDA lesion, a similar distribution

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was found in all regions except the rostral neostriatum. Both the lesioned and control rats showed some preferential labeling of the choroid plexus, in spite of incubation in the presence of 30 nM cold serotonin. However, there was no significant labeling in the substantia nigra.

The increased [^{125}I]DOI binding associated with 5-HT hyperinnervation in the rostral neostriatum eliminated the normally observed caudorostral decreasing gradient in the density of these receptors.[82] This increase of 5-HT_{2A} receptors was reminiscent of that reported in the 5-HT-hyperinnervated inferior olivary complex of adult rat following cytotoxic lesioning of its 5-HT innervation with 5,6-dihydroxytryptamine.[19] In this latter study, the 5-HT_{2A} receptor increase had been interpreted as the result of an up-regulation without ruling out the possibility that it be due to the initial 5-HT denervation rather than to the ensuing 5-HT hyperinnervation. In the present study, 5-HT denervation was no longer in question as the cause of the 5-HT_{2A} up-regulation. Moreover, the 5-HT_{2A} receptor increase seemed tightly related to the 5-HT hyperinnervation in view of the coinciding anatomical distribution of the two phenomena. Yet, it is well established that this 5-HT receptor subtype is essentially postsynaptic to 5-HT neurons.[83] Interestingly, it was also demonstrated recently that in the neonatally DA-denervated and 5-HT–hyperinnervated neostriatum—but not in its adult counterpart without 5-HT hyperinnervation nor changes in 5-HT_{2A} receptor binding—neuronal responsiveness to the iontophoretic application of 5-HT and to the 5-$HT_{2A/2C}$ receptor agonist DOI is also considerably increased.[71]

SUMMARY AND CONCLUSIONS

The destruction of nigrostriatal DA neurons by cerebroventricular injection of 6-OHDA in newborn rat results in a nearly complete DA denervation of the neostriatum and its subsequent 5-HT hyperinnervation. Three to six months after the neonatal 6-OHDA lesion, D_1 receptors are slightly decreased in the rostral neostriatum, but unchanged in its caudal half and in the substantia nigra. In contrast, D_2 receptors are increased throughout the neostriatum and decreased in the substantia nigra. Interestingly, no parallel changes occur in D_2 receptor mRNA, as measured by *in situ* hybridization on adjacent sections. The responsiveness to DA and to the D_1 receptor agonist SKF 38393 is markedly enhanced,[24] suggesting that this hypersensitivity is independent of the ligand recognition sites but rather mediated by postreceptor transducing mechanisms. On the other hand, the responsiveness to the D_2 receptor agonist PPHT remains unchanged in spite of the up-regulation of neostriatal D_2 receptors. The opposite changes in the number of D_1 and D_2 binding sites, dissociated from the expression of D_2 receptor mMRNA and from the sensitivity to DA receptor agonists, suggest independent adaptations triggered by the neonatal DA denervation and/or ensuing 5-HT hyperinnervation.

With regard to 5-HT receptor subtypes, a considerable increase in 5-HT_{1B} binding sites in both the rostral and caudal neostriatum, as well as in the substantia nigra and globus pallidus, suggests an up-regulation and increased axonal transport of these receptors in neostriatal projection neurons. A similar increase in the density of 5-HT_{1nonAB} receptors in the two halves of neostriatum and in the substantia nigra, but not the globus pallidus, presumably reflects an up-regulation and transport of the corresponding receptors (5-HT_{1D} and 5-HT_{2C}) in striatonigral projection neurons only. The distribution of both increases throughout the neostriatum suggest a possible role of DA in the regulation of these receptors during ontogenesis. The even greater increase in 5-HT_{2A} receptor density predominating in the rostral, 5-HT-hyperinnervated part of the neostriatum suggests a tight relationship with the 5-HT

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innervation. These increases in 5-HT receptor density can be correlated with an enhanced electrophysiological responsiveness[72] of neostriatal neurons to the iontophoretic application of 5-HT and its agonists, *m*CPP and DOI. They could therefore account for an enhancement of 5-HT neurotransmission in the neonatally 6-OHDA-denervated and 5-HT-hyperinnervated neostriatum, even if basal extracellular 5-HT levels remain normal under these conditions due to an increased number of 5-HT uptake sites.[84]

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